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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/054,710	01/22/2002	Koichi Masuda	047940-0119	5419

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EXAMINER	
DAVIS, RUTH A	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 01/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/054,710	MASUDA ET AL.	
	Examiner	Art Unit	
	Ruth A. Davis	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *15,16,31 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,17-30 and 33-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response filed on October 31, 2005 has been received and entered into the case. The affidavit submitted on October 31 has also been received and entered into the case. Claims 1 – 35 are pending; claims 15 – 16 and 31 – 32 have been withdrawn from consideration; claims 1 – 14, 17 – 30 and 33 – 35 have been considered on the merits. All arguments and the affidavit have been fully considered.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1 – 14, 17 – 30 and 33 – 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification as originally filed, in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1 and 17 recite the limitation "but short enough such that the collagen fibrils in the cell associated matrix do not become overly crosslinked", which is not described in the specification as originally filed. While the specification does disclose that culture times, in general, can determine the degree of crosslinking in the cell associated matrix, the specification

fails to disclose a method of culturing the cells for a time period short enough such that the matrix does not become overly crosslinked. This is a new matter rejection.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1 – 14, 17 – 30 and 33 – 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 17 and their dependents are rendered vague and indefinite for reciting "do not become overly crosslinked" because it is unclear to what degree of crosslinking applicant regards as "overly crosslinked". Applicant fails to define an amount of crosslinking that is desirable, or not, such that one in the art would know how much is "overly crosslinked".

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1 – 8, 10, 14, 17 – 24, 26, 29 – 30 and 33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kai in view of Masuda.

Applicant claims a method for determining the effect of a test agent on a tissue engineered cartilage matrix, the method comprising culturing an engineered cartilage tissue (ECT), contacting test agents with cells or tissues of the ECT, and measuring the effect that the agents have on the ECT or cells thereof; wherein the matrix is cultured to be rapidly degraded losing about half of its proteoglycan content within 24 hours when treated withIL-1 and wherein the loss of proteoglycan can be measured without radioactive agents. The ECT is cultured by culturing isolated chondrogenic cells for a time sufficient to form a chondrogenic cell-associated matrix, and culturing the cells with the cell-associated matrix on a semipermeable membrane in the presence of a growth factor for a time sufficient to form an ECT. The cells or tissues are selected from isolated chondrogenic cells, the chondrogenic cells during culture, the cells and cell-associated matrix before or after culturing, and the ECT. Alternatively, the cells are selected from isolated chondrogenic cells, the chondrogenic cells during culture, the cells and cell-associated matrix before or after culturing, and the ECT in the presence of a known modulator of cartilage tissue. The chondrogenic cell-associated matrix comprises aggrecan, collagen types II,

IX, XI, matrix proteins, and hyaluronan and the ECT comprises collagens II, IX, XI, hyaluronan, and at least about 5 mg/cc3 aggrecan, the ratio of aggrecan : hyaluronan is about 10:1 – 200:1, and the ration of aggrecan : collagen is about 1:1 – 10:1. The isolated chondrogenic cells are isolated from articular cartilage, costal, nasal, auricular, tracheal, epiglottic, thyroid, arytenoids or cricoid cartilages, specifically fibrocartilage from ligament, tendon, meniscus, or intervertebral disc. The chondrogenic cells are cultured on an alginate medium, the measuring is performed without addition of extrinsic radioactivity and the method further comprises identifying one or more test agents that have desirable characteristics and producing the agents as a therapeutic drug. The modulator of the ECT tissue is a matrix stimulating agent, cytokine or TNF-alpha wherein the cytokine is interleukin 1 (IL-1).

Kai teaches a method for determining effects of agents on cartilage, wherein the cartilage is cultured with IL-1 or TNF, is contacted with the test agent, and is measured for effects of the test agent (abstract). The method is used to screen for therapeutic agents (abstract).

Kai does not teach the method wherein the cartilage is cultured in the manner claimed. However, Masuda teaches methods for culturing an engineered cartilage tissue, wherein isolated chondrocytes are cultured in alginate for a time to allow a cell associated matrix to form (col.4 line 30-35). The cell associated matrix has at least about 5 mg/cc3 aggrecan, a ratio of aggrecan to hyaluronan of 10:1 to 200:1, and a ratio of aggrecan to collagen of about 1:1 to 10: (col.4 line 35-40). The chondrogenic cells are cultured on a semi-permeable membrane in the presence of growth factors (col. 4 line 44-46). The chondrocytes may be isolated from articular cartilage, fibrocartilage, costal, nasal, auricular, tracheal, epiglottic, thyroid, arytenoid or cricoid cartilages (col.5 line 31-38) and the resulting matrix comprises aggrecan, collagn II, IX, XI and hyaluronan

(col.6 line 61-64). At the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to culture the cartilage of Kai using the methods of Masuda because it was a known method for culturing cartilage tissues. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by common culture practices in the art to culture the cartilage of Kai via the methods of Masuda with a reasonable expectation for successfully determining the effects of test agents on cartilage cultures. Although Masuda does not teach the fibrocartilage is from a ligament, tendon, meniscus or intervertebral discs, they were each well known sources of fibrocartilage. Moreover at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to use any of the above sources as the source of fibrocartilage in the methods of Masuda.

8. Claims 1 – 10, 17 – 26, 33 and 35 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Purchio in view of Masuda.

Applicant claims a method for determining the effect of a test agent on a tissue engineered cartilage matrix, the method comprising culturing an engineered cartilage tissue (ECT), contacting test agents with cells or tissues of the ECT, and measuring the effect that the agents have on the ECT or cells thereof; wherein the matrix is cultured to be rapidly degraded losing about half of its proteoglycan content within 24 hours when treated withIL-1 and wherein the loss of proteoglycan can be measured without radioactive agents. The ECT is cultured by culturing isolated chondrogenic cells for a time sufficient to form a chondrogenic cell-associated matrix, and culturing the cells with the cell-associated matrix on a semipermeable membrane in the presence of a growth factor for a time sufficient to form an ECT. The cells or tissues are

selected from isolated chondrogenic cells, the chondrogenic cells during culture, the cells and cell-associated matrix before or after culturing, and the ECT. Alternatively, the cells are selected from isolated chondrogenic cells, the chondrogenic cells during culture, the cells and cell-associated matrix before or after culturing, and the ECT in the presence of a known modulator of cartilage tissue. The chondrogenic cell-associated matrix comprises aggrecan, collagen types II, IX, XI, matrix proteins, and hyaluronan and the ECT comprises collagens II, IX, XI, hyaluronan, and at least about 5 mg/cc3 aggrecan, the ratio of aggrecan : hyaluronan is about 10:1 – 200:1, and the ration of aggrecan : collagen is about 1:1 – 10:1. The isolated chondrogenic cells are isolated from articular cartilage, costal, nasal, auricular, tracheal, epiglottic, thyroid, arytenoids or cricoid cartilages, specifically fibrocartilage from ligament, tendon, meniscus, or intervertebral disc. The chondrogenic cells are cultured on an alginate medium, the measuring comprises measuring the amount of proteoglycan in the ECT, is performed without addition of extrinsic radioactivity and the method further comprises identifying one or more test agents that have desirable characteristics and producing the agents as a therapeutic drug. The culturing of ECT and the contacting the cells with the test agent occurs in the same well of a multi-well plate.

Purchio teaches methods for screening effects of test agents on cartilage cultures wherein the cultures are exposed to the test agents and the effects are measured (col.16 line 12-22). Examples of such effects include the amount of proteoglycan (col.16 line 27-34). Specifically, chondrocytes are harvested from articular cartilage and cultured in multi-well plates (col.21 lines 18-60) and the test agents are identified for therapeutic and/or pharmaceutical compounds (col. 16). Purchio teaches that the chondrocytes can be isolated from articular or costal cartilage (col.11 line 62-65).

Purchio does not teach the method wherein the cartilage is cultured in the manner claimed. However, Masuda teaches methods for culturing an engineered cartilage tissue, wherein isolated chondrocytes are cultured in alginate for a time to allow a cell associated matrix to form (col.4 line 30-35). The cell associated matrix has at least about 5 mg/cc3 aggrecan, a ratio of aggrecan to hyaluronan of 10:1 to 200:1, and a ratio of aggrecan to collagen of about 1:1 to 10: (col.4 line 35-40). The chondrogenic cells are cultured on a semi-permeable membrane in the presence of growth factors (col. 4 line 44-46). The chondrocytes may be isolated from articular cartilage, fibrocartilage, costal, nasal, auricular, tracheal, epiglottic, thyroid, arytenoid or cricoid cartilages (col.5 line 31-38) and the resulting matrix comprises aggrecan, collagn II, IX, XI and hyaluronan (col.6 line 61-64). At the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to culture the cartilage of Purchio using the methods of Masuda because it was a known method for culturing cartilage tissues. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by common culture practices in the art to culture the cartilage of Purchio via the methods of Masuda with a reasonable expectation for successfully determining the effects of test agents on cartilage cultures. Although Masuda does not teach the fibrocartilage is from a ligament, tendon, meniscus or intervertebral discs, they were each well known sources of fibrocartilage. Moreover at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to use any of the above sources as the source of fibrocartilage in the methods of Masuda.

9. Claims 1 – 8, 17 – 24, 29 – 30 and 35 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Saito in view of Masuda.

Applicant claims a method for determining the effect of a test agent on a tissue engineered cartilage matrix, the method comprising culturing an engineered cartilage tissue (ECT), contacting test agents with cells or tissues of the ECT, and measuring the effect that the agents have on the ECT or cells thereof; wherein the matrix is cultured to be rapidly degraded losing about half of its proteoglycan content within 24 hours when treated withIL-1 and wherein the loss of proteoglycan can be measured without radioactive agents. The ECT is cultured by culturing isolated chondrogenic cells for a time sufficient to form a chondrogenic cell-associated matrix, and culturing the cells with the cell-associated matrix on a semipermeable membrane in the presence of a growth factor for a time sufficient to form an ECT. The cells or tissues are selected from isolated chondrogenic cells, the chondrogenic cells during culture, the cells and cell-associated matrix before or after culturing, and the ECT. Alternatively, the cells are selected from isolated chondrogenic cells, the chondrogenic cells during culture, the cells and cell-associated matrix before or after culturing, and the ECT in the presence of a known modulator of cartilage tissue. The chondrogenic cell-associated matrix comprises aggrecan, collagen types II, IX, XI, matrix proteins, and hyaluronan and the ECT comprises collagens II, IX, XI, hyaluronan, and at least about 5 mg/cc3 aggrecan, the ratio of aggrecan : hyaluronan is about 10:1 – 200:1, and the ration of aggrecan : collagen is about 1:1 – 10:1. The isolated chondrogenic cells are isolated from articular cartilage, costal, nasal, auricular, tracheal, epiglottic, thyroid, arytenoids or cricoid cartilages, specifically fibrocartilage from ligament, tendon, meniscus, or intervertebral disc. The chondrogenic cells are cultured on an alginate medium. The modulator

of the ECT tissue is a matrix stimulating agent, cytokine or TNF-alpha wherein the cytokine is interleukin 1 (IL-1). Finally, the culturing and contacting step occur in the same well of a multi well plate.

Saito teaches culturing cartilage in multi well plates in the presences of IL-1 alpha, wherein the effects of the test agent were measured (p.727).

Saito does not teach the method wherein the cartilage is cultured in the manner claimed. However, Masuda teaches methods for culturing an engineered cartilage tissue, wherein isolated chondrocytes are cultured in alginate for a time to allow a cell associated matrix to form (col.4 line 30-35). The cell associated matrix has at least about 5 mg/cc3 aggrecan, a ratio of aggrecan to hyaluronan of 10:1 to 200:1, and a ratio of aggrecan to collagen of about 1:1 to 10: (col.4 line 35-40). The chondrogenic cells are cultured on a semi-permeable membrane in the presence of growth factors (col. 4 line 44-46). The chondrocytes may be isolated from articular cartilage, fibrocartilage, costal, nasal, auricular, tracheal, epiglottic, thyroid, arytenoid or cricoid cartilages (col.5 line 31-38) and the resulting matrix comprises aggrecan, collagn II, IX, XI and hyaluronan (col.6 line 61-64). At the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to culture the cartilage of Saito using the methods of Masuda because it was a known method for culturing cartilage tissues. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by common culture practices in the art to culture the cartilage of Saito via the methods of Masuda with a reasonable expectation for successfully determining the effects of test agents on cartilage cultures. Although Masuda does not teach the fibrocartilage is from a ligament, tendon, meniscus or intervertebral discs, they were each well known sources of fibrocartilage. Moreover at the time

of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to use any of the above sources as the source of fibrocartilage in the methods of Masuda.

10. Claims 1 – 11, 17 – 27 and 29 – 30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Huch in view of Masuda.

Applicant claims a method for determining the effect of a test agent on a tissue engineered cartilage matrix, the method comprising culturing an engineered cartilage tissue (ECT), contacting test agents with cells or tissues of the ECT, and measuring the effect that the agents have on the ECT or cells thereof; wherein the matrix is cultured to be rapidly degraded losing about half of its proteoglycan content within 24 hours when treated withIL-1 and wherein the loss of proteoglycan can be measured without radioactive agents. The ECT is cultured by culturing isolated chondrogenic cells for a time sufficient to form a chondrogenic cell-associated matrix, and culturing the cells with the cell-associated matrix on a semipermeable membrane in the presence of a growth factor for a time sufficient to form an ECT. The cells or tissues are selected from isolated chondrogenic cells, the chondrogenic cells during culture, the cells and cell-associated matrix before or after culturing, and the ECT. Alternatively, the cells are selected from isolated chondrogenic cells, the chondrogenic cells during culture, the cells and cell-associated matrix before or after culturing, and the ECT in the presence of a known modulator of cartilage tissue. The chondrogenic cell-associated matrix comprises aggrecan, collagen types II, IX, XI, matrix proteins, and hyaluronan and the ECT comprises collagens II, IX, XI, hyaluronan, and at least about 5 mg/cc3 aggrecan, the ratio of aggrecan : hyaluronan is about 10:1 – 200:1, and the ration of aggrecan : collagen is about 1:1 – 10:1. The isolated chondrogenic cells are

isolated from articular cartilage, costal, nasal, auricular, tracheal, epiglottic, thyroid, arytenoids or cricoid cartilages, specifically fibrocartilage from ligament, tendon, meniscus, or intervertebral disc. The chondrogenic cells are cultured on an alginate medium, the measuring comprises measuring the amount of proteoglycan in the ECT, enzymatically degrading the ECT and is performed without addition of extrinsic radioactivity. The method further comprises identifying one or more test agents that have desirable characteristics and producing the agents as a therapeutic drug. The culturing of ECT and the contacting the cells with the test agent occurs in the same well of a multi-well plate. The modulator of the ECT tissue is a matrix stimulating agent, cytokine or TNF-alpha wherein the cytokine is interleukin 1.

Huch teaches methods for culturing articular chondrocytes in an alginate medium in the presence of a test agent, IL-1, wherein proteoglycan was measured (abstract). Specifically, the cartilage was degraded with enzymes, the chondrocytes were cultured with alginate in a multi-well plate in the presence of IL-1, and the amount of proteoglycan was measured (p. 2158).

Huch does not teach the method wherein the cartilage is cultured in the manner claimed. However, Masuda teaches methods for culturing an engineered cartilage tissue, wherein isolated chondrocytes are cultured in alginate for a time to allow a cell associated matrix to form (col.4 line 30-35). The cell associated matrix has at least about 5 mg/cc3 aggrecan, a ratio of aggrecan to hyaluronan of 10:1 to 200:1, and a ratio of aggrecan to collagen of about 1:1 to 10: (col.4 line 35-40). The chondrogenic cells are cultured on a semi-permeable membrane in the presence of growth factors (col. 4 line 44-46). The chondrocytes may be isolated from articular cartilage, fibrocartilage, costal, nasal, auricular, tracheal, epiglottic, thyroid, arytenoid or cricoid cartilages (col.5 line 31-38) and the resulting matrix comprises aggrecan, collagn II, IX, XI and hyaluronan

(col.6 line 61-64). At the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to culture the cartilage of Huch using the methods of Masuda because it was a known method for culturing cartilage tissues. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by common culture practices in the art to culture the cartilage of Huch via the methods of Masuda with a reasonable expectation for successfully determining the effects of test agents on cartilage cultures. Although Masuda does not teach the fibrocartilage is from a ligament, tendon, meniscus or intervertebral discs, they were each well known sources of fibrocartilage. Moreover at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to use any of the above sources as the source of fibrocartilage in the methods of Masuda.

11. Claims 1 – 8, 10, 14, 17 – 24, 26 and 33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lansbury in view of Masuda.

Applicant claims a method for determining the effect of a test agent on a tissue engineered cartilage matrix, the method comprising culturing an engineered cartilage tissue (ECT), contacting test agents with cells or tissues of the ECT, and measuring the effect that the agents have on the ECT or cells thereof; wherein the matrix is cultured to be rapidly degraded losing about half of its proteoglycan content within 24 hours when treated withIL-1 and wherein the loss of proteoglycan can be measured without radioactive agents. The ECT is cultured by culturing isolated chondrogenic cells for a time sufficient to form a chondrogenic cell-associated matrix, and culturing the cells with the cell-associated matrix on a semipermeable membrane in the presence of a growth factor for a time sufficient to form an ECT. The cells or tissues are

selected from isolated chondrogenic cells, the chondrogenic cells during culture, the cells and cell-associated matrix before or after culturing, and the ECT. Alternatively, the cells are selected from isolated chondrogenic cells, the chondrogenic cells during culture, the cells and cell-associated matrix before or after culturing, and the ECT in the presence of a known modulator of cartilage tissue. The chondrogenic cell-associated matrix comprises aggrecan, collagen types II, IX, XI, matrix proteins, and hyaluronan and the ECT comprises collagens II, IX, XI, hyaluronan, and at least about 5 mg/cc3 aggrecan, the ratio of aggrecan : hyaluronan is about 10:1 – 200:1, and the ration of aggrecan : collagen is about 1:1 – 10:1. The isolated chondrogenic cells are isolated from articular cartilage, costal, nasal, auricular, tracheal, epiglottic, thyroid, arytenoids or cricoid cartilages, specifically fibrocartilage from ligament, tendon, meniscus, or intervertebral disc. The chondrogenic cells are cultured on an alginate medium, the measuring is performed without addition of extrinsic radioactivity and the method further comprises identifying one or more test agents that have desirable characteristics and producing the agents as a therapeutic drug.

Lansbury teaches methods for screening the effects of agents on cartilage cultures wherein a chondrocyte cell culture is incubated (or contacted) with the test agent and the effects are measured (claim 34). The method is used to identify agents with desirable, therapeutic characteristics, specifically the ability to repair damaged cartilage (claim 34).

Lansbury does not teach the method wherein the cartilage is cultured in the manner claimed. However, Masuda teaches methods for culturing an engineered cartilage tissue, wherein isolated chondrocytes are cultured in alginate for a time to allow a cell associated matrix to form (col.4 line 30-35). The cell associated matrix has at least about 5 mg/cc3 aggrecan, a

ratio of aggrecan to hyaluronan of 10:1 to 200:1, and a ratio of aggrecan to collagen of about 1:1 to 10: (col.4 line 35-40). The chondrogenic cells are cultured on a semi-permeable membrane in the presence of growth factors (col. 4 line 44-46). The chondrocytes may be isolated from articular cartilage, fibrocartilage, costal, nasal, auricular, tracheal, epiglottic, thyroid, arytenoid or cricoid cartilages (col.5 line 31-38) and the resulting matrix comprises aggrecan, collagn II, IX, XI and hyaluronan (col.6 line 61-64). At the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to culture the cartilage of Lansbury using the methods of Masuda because it was a known method for culturing cartilage tissues. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by common culture practices in the art to culture the cartilage of Lansbury via the methods of Masuda with a reasonable expectation for successfully determining the effects of test agents on cartilage cultures. Although Masuda does not teach the fibrocartilage is from a ligament, tendon, meniscus or intervertebral discs, they were each well known sources of fibrocartilage. Moreover at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to use any of the above sources as the source of fibrocartilage in the methods of Masuda.

Response to Arguments

Applicant argues that the references do not teach each of the claimed limitations. Specifically that the references do not teach the claimed culturing times, use of the culture, and that the proteoglycan content can be measured without radioactive agents. Applicant

additionally argues that the culture of Masuda is not the same as claimed, since the culture times are different and that the rapid degradation is not inherent due to differing culture times. Applicant further relies upon an affidavit, which reiterates the above.

However, these arguments and affidavit fail to persuade for the following reasons:

Regarding the culturing times, it is first pointed out that the methods of the instant application culture the ECM using the methods of Masuda (examples). It is further noted that the methods of Masuda have culture times of 3 days (col.8) or 7 – 14 days (examples), which is the same as the instant disclosure. Thus it is maintained that the methods of culture, to include culturing times, are the same as that disclosed by Masuda.

Further, while Masuda may not use the culture for the same purpose, it is noted that the primary references recite method for determining the effects of test agents on cartilage tissues using engineered tissues. Thus the methods of use are well known in the art, as evidenced by the cited references.

Regarding applicant's assertions that the proteoglycan content can not be measured without radioactive agents, it is first pointed out that the claims to not require the proteoglycan content be measured without radioactive agents, but that it is possible to measure the content without radioactive agents. Furthermore, since the cultured tissues of Masuda and the instant claims are made in the same manner, any unrecognized trait of that culture would be inherent to the tissues of Masuda. Thus, the tissues of Masuda must also have the ability to measure loss of proteoglycan content without radioactive agents.

In addition, regarding applicant's assertions that the instant cartilage tissue is different from that of Masuda, applicant is reminded that previously applicant expressly states:

"Applicants have recognized a previously unappreciated trait found in select samples of engineered cartilage tissues disclosed by Masuda et al." In the instant case it is unequivocal that the engineered cartilage tissue of applicant's claims is cultured under the same conditions as disclosed in the prior art. Because the same culture conditions are used to make the engineered tissues, the resulting properties of that tissue must necessarily be the same as disclosed by applicant. Otherwise applicant's invention could not function as disclosed. MPEP § 2112 clearly states: "The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness".

Regarding applicant's argument that Masuda does not require the tissues be cultured in the manner instantly claimed, Masuda still teaches the claimed method of culturing, therefore the method is clearly taught and suggested by Masuda.

Regarding applicant's assertion that a new trait has been discovered in only some of the cartilage tissues of Masuda, "the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by

a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency) (MPEP 2112)

Regarding applicant's argument that the ECM of Masuda changes with culture time thus cannot be used in the claimed method, it is noted that the claims do not require a specific culture time, thus the argument is not commensurate in scope with the claims. Even still, the claims are directed to an ECM cultured by the same methods taught and disclosed by Masuda. Since Masuda clearly teaches the same culture conditions as claimed, the tissues of Masuda must also, intrinsically exhibit the claimed properties, even though they were not previously recognized.

Therefore, since the references clearly teach methods for determining effects of test agents on engineered cartilage tissue, and the method of culturing such engineered cartilage tissues is disclosed by Masuda, the claims stand rejected as being obvious for these reasons and those stated in the rejections above.

Conclusion

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruth A. Davis whose telephone number is 571-272-0915. The examiner can normally be reached on M-F 7:00 - 2:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ruth A. Davis
January 13, 2006
AU 1651